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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/817,507	04/17/1997	TADAMITSU KISHIMOTO	53466/201	8301

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EXAMINER	
CANELLA, KAREN A	
ART UNIT	PAPER NUMBER
1642	4

DATE MAILED: 08/11/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action

Application No.	Applicant(s)
08/817,507	Kishimoto
Examiner	**Art Unit**
Karen Canella	1642

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED *Jun 18, 2003* FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid the abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

THE PERIOD FOR REPLY [check only a) or b)]

a) ☒ The period for reply expires *3 months* months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection. ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1. ☐ A Notice of Appeal was filed on _____. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.

2. ☐ The proposed amendment(s) will not be entered because:

(a) ☐ they raise new issues that would require further consideration and/or search (see NOTE below);

(b) ☐ they raise the issue of new matter (see NOTE below);

(c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

(d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

NOTE: _____

3. ☒ Applicant's reply has overcome the following rejection(s):
see attached

4. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

5. ☒ The a) ☐ affidavit, b) ☐ exhibit, or c) ☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because:
see attached

6. ☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

7. ☒ For purposes of Appeal, the proposed amendment(s) a) ☐ will not be entered or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

The status of the claim(s) is (or will be) as follows:

Claim(s) allowed: *none*

Claim(s) objected to: _____

Claim(s) rejected: *15 and 24-28*

Claim(s) withdrawn from consideration: _____

8. ☐ The proposed drawing correction filed on _____ is a) ☐ approved or b) ☐ disapproved by the Examiner.

9. ☐ Note the attached Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____.

10. ☐ Other:

Response to Argument

1. The rejection of claims 15 and 24-28 under 35 U.S.C. 103(a) as being unpatentable over Emilie et al (Blood, 1994, Vol. 84, pp. 2472-2479) in view of Sato et al (Cancer Research, 1993, Vol. 53, pp. 851-856) is maintained for reasons of record.

Emilie et al teach the alleviation of the symptoms of cachexia in human patients by a method comprising the administration of an antibody which binds to Il-6. Emilie et al do not teach the administration of antibodies to the IL-6 receptor. Sato et al teach the humanized PM-1 antibody which binds to the Il-6 receptor, and the administration of said antibody to treat interleukin-6-dependent tumor growth, wherein the administration of said antibody is effective in blocking signal transduction by the Il-6 receptor. It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to use the method taught by Sato et al as a method of treating cachexia in a human patient. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Sato on the in vitro efficacy of the humanized PM-1 antibody in blocking of Il-6 mediated signal transduction in human cells by binding to the Il-6 receptor, and the teachings of Emilie et al preventing the activation of the Il-6 receptor by binding the ligand for the Il-6 receptor with an anti-Il-6 antibody.

Applicant argues that none of the prior art references qualifies as an inherent disclosure of the suppression of elevated levels ionized calcium in the blood. Applicant states that the examiner must provide a basis in fact and/or technical reasoning to support the allegedly inherent characteristic that flows from the teachings of the prior art. Applicant states that there is no teaching or indication in either Emilie or Sato that cachexia is always accompanied by an elevation in ionized calcium in the blood and that none of the prior art references teach or suggest any relationship between hypercalcemia and Il-6. Applicant refers to In re Robertson which states that the missing descriptive matter is necessarily present in the thing described by the

reference and states that the probability of a certain characteristic in the prior art is not sufficient to establish the inherency of that result or characteristic. Applicant ends the argument by pointing out that there is no motivation to use an antibody to Il-6 in order to treat cachexia and again recites the fact that Emilie teaches an antibody to Il-6, not to the Il-6 receptor, a fact which is well known to the examiner. All these arguments have been considered but not found persuasive.

The M.P.E.P. (2141.02) states "In determining whether the invention as a whole would have been obvious under 35 U.S.C. 103, we must first delineate the invention as a whole. In delineating the invention as a whole, we look not only to the subject matter which is literally recited in the claim in question... but also to those properties of the subject matter which are inherent in the subject matter and are disclosed in the specification". The art teaches that individuals suffering from cachexia can benefit by the reduction in circulating Il-6 levels by means of an antibody which binds to Il-6. One of skill in the art would recognize that the binding of the administered anti-Il-6 antibody to the circulating Il-6 would decrease the amount of free Il-6 available to bind with the Il-6 receptor, and that the ultimate effect of Il-6 as a cytokine, is to bind to the Il-6 receptor of the surface of cells, thereby causing a signal to be transmitted to said cells. The elimination of high levels of Il-6 in the blood stream by means of the anti-Il-6 antibody would result in less signal being transmitted to cells bearing the Il-6 receptor. Sato et al teach the humanized PM-1 antibody which binds to the Il-6 receptor . It is noted that on page 4, lines 14-15 of the instant specification that the PM-1 antibody is disclosed as an antibody to carry out the instant method claims. Sato et al teaches that antibodies which inhibit Il-6 functions are expected to be useful therapeutic agents in patients. Sato teaches that PM-1 antibody which binds to the Il-6 receptor inhibits Il-6 function. Thus, one of skill in the art would be motivated to treat cachexia by administration of the humanized PM-1 antibody as taught by Sato in order to inhibit IL-6 function by the binding of the PM-1 antibody to the Il-6 receptor, as excess Il-6, and therefore excess Il-6 function by means of binding to the Il-6

receptor as taught to be the target of therapeutic intervention in the treatment of cachexia as taught by Emilie. The specification does not set forth antibodies to the Il-6 receptor which differ from the prior art antibodies. Thus, the administration of the prior art antibodies to a person suffering from cachexia would result in the same reduction of ionized calcium levels as claimed because there is no difference in the disclosed treatment steps which are rendered obvious from the prior art. The binding of the PM-1 antibody to the Il-6 receptor of the prior art will have the same effect in a person suffering from cachexia as the instant claimed method, which specifies that reduction of ionized calcium levels will occur. Thus the reduction in ionized calcium levels is inherent in the method rendered obvious by the prior art.

2. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen Canella whose telephone number is (703) 308-8362. The examiner can normally be reached on Monday through Friday from 8:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Karen A. Canella

Karen A. Canella, Ph.D.

Patent Examiner, Group 1642

August 7, 2003